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To assess the role of immune infiltrating immune cells of patients with chronic heart failure with atrial fibrillation and nursing care in these patients

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ABSTRACT

This research aimed to assess the role of immune infiltrating immune cells of patients with chronic heart failure with atrial fibrillation and nursing care in these patients. For this aim, 400 patients from 22 centres across our nations were recruited in the index cohort based on worsening signs/symptoms and poor management of HF. The validation cohort consisted of patients who had previously participated in the index cohort. The primary goal was to reduce all-cause mortality as well as unscheduled hospitalisations due to heart failure. Hospitalizations for heart failure (HF), total mortality, and death attributable to cardiovascular disease were secondary objectives. Results showed that interleukin-6 (IL-6) levels in patients ranged from 3.1 to 11.21 pg/mL on average, with 228 patients (or 57% of the total) having IL-6 levels that were higher than the 95th percentile of normal values (> 4.45 pg/mL). The average age of the group was 69.85±9.68 years, and there were 295 males in the group (73.75 percent). 17 Patients who had higher levels of IL-6 tended to be older, more frequently suffered from heart failure with preserved ejection fraction (HFpEF), and more frequently suffered from anaemia, diabetes, and atrial fibrillation. Patients who had higher levels of IL-6 also had a greater likelihood of suffering from these conditions. Patients who had higher levels of IL-6 also had a shorter distance travelled during the 6MWT and had a lower chance of completing the test. Both test completion [OR (95% CI) per doubling of IL-6: 0.81 (0.71 - 0.91), P< 0.001] and total distance covered [B (95% CI) per doubling of IL-6: 28.11 (32.58 to-21.98), P< 0.001] were negatively associated with increasing levels of IL-6, Patients who had high levels of IL-6 had higher median hepcidin levels than patients who had low levels of IL-6. This was discovered by comparing the two groups' hepcidin levels. There was a correlation between increased levels of IL-6 and increased levels of NT-proBNP and CRP, as well as a reduction in eGFR. In conclusion, independent predictors of IL-6 were younger age, high-flow partial ejection fraction (HFpEF), atrial fibrillation (AF), iron insufficiency, and higher levels of NT-proBNP, PCT, hepcidin, and TNF-/IL-1 related biomarkers. Last but not least, IL-6 levels in the plasma were able to predict death and/or hospitalisation due to HF on their own, although they did not contribute to differentiation in prior models.

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Introduction

It is impossible to place an adequate amount of emphasis on the significance of inflammation as a contributor to the condition known as heart failure (HF). Patients who were diagnosed with heart failure and had greater levels of pro-inflammatory cytokines had worse outcomes and more severe cardiac remodelling than patients who did not have these elevated levels (1). The majority of larger clinical studies that targeted tumour necrosis factor (TNF), such as the ATTACH and RENEWAL trials, were found to be ineffective. In spite of this, the ATTACH research did not investigate the likelihood of adverse effects associated with greater doses of infliximab. In spite of this, there were indications of some benefits in the study that was done on immunomodulatory drugs and HF, even if it was limited (1, 2). However, the recent Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) demonstrated unprecedented benefits in reduced cardiovascular (CV) risk by evaluating the effects of interleukin (IL)-1 blockade in patients who had previously suffered a myocardial infarction and had elevated levels of high-sensitivity C-reactive protein. This study was conducted in patients who had undergone an evaluation of the effects of interleukin (IL)-1 blockade in patients who the purpose of this research was to evaluate whether or not individuals who had previously had a myocardial infarction and had excessive levels of high cholesterol were at an increased risk for developing coronary artery disease (hsCRP) (3). As a consequence of CANTOS and other studies that point to the importance of inflammation in the progression of HF, there has been a resurgence of interest in the use of anti-inflammatory medications in the treatment of HF. This might be a viable therapeutic strategy.

Interleukin-6 is an example of a cytokine that has the potential to act in both a pro-inflammatory and anti-inflam-

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matory way (4). The relevance of interleukin-6 (IL-6) to cardiovascular disease has just recently come to be understood in its entirety throughout the span of a span of time that is very recent. The single nucleotide polymorphism (SNP) known as Asp358Ala, which is found in the IL-6 receptor, was the subject of a comprehensive meta-analysis. Those who had the Asp358Ala variation had a coronary artery disease risk that was 3.4% lower than that of those who did not have the variant (5). This adds to the increasing body of evidence that suggests IL-6 signalling may have a causal role in the development of atherosclerosis. In addition, there is a correlation between age and a rise in IL-6 levels, and signalling from IL-6 has been linked to the pathophysiology of frequent HF co-morbidities such as frailty, chronic illness, anaemia, renal disease, and atrial fibrillation (AF) (6-9).

Increased levels of interleukin-6 (IL-6) and IL-6 receptor messenger RNA (mRNA) in the heart have been linked to the development of heart failure. This has been linked to changes in the haemodynamics of the patient. In addition to the CG genotype of the 174G/C SNP of the IL-6 promoter, and independent of left ventricular ejection fraction, circulating levels of IL-6 were also connected with worsening HF. This was the case regardless of whether or not the patient had a normal left ventricular ejection fraction. This was the case regardless of whether or not the patient's left ventricular ejection % was normal or lowered (LVEF) (10 – 12). In addition, significant correlations between IL-6 and death rates linked with heart failure have been discovered in some patient populations that suffer heart failure. These populations are on the lower end of the scale (13, 14). They are of particular interest in the treatment of HF because pharmaceutical treatments that target IL-6 signalling have already been developed and successfully utilised in the treatment of a wide variety of (autoimmune) disorders (for example, tocilizumab, sarilumab, and siltuxumab), as recently reviewed by Garbers et al (15-16).

On the other hand, inflammation is a complex illness process that includes a number of different signalling systems and key mediators. This is because inflammation may result from a variety of different diseases. As a consequence of this, it is of the utmost importance to examine the relationship that exists between IL-6 and the many biomarkers that may be found in HF. These studies did not evaluate whether or not IL-6 was associated with any other biomarkers, and they did not include adequate numbers of subjects in their samples. As a consequence of this, we made the decision to do research on the matter by analysing the relationship that exists between IL-6 and the clinical features, outcomes, and other biomarkers that are linked with HF.

Materials and Methods

400 patients from 22 centres across our nations were recruited in the index cohort based on worsening signs/symptoms and poor management of HF. The validation cohort consisted of patients who had previously participated in the index cohort. The primary goal was to reduce all-cause mortality as well as unscheduled hospitalisations due to heart failure. Hospitalizations for heart failure (HF), total mortality, and death attributable to cardiovascular disease were secondary objectives. The conclusions about specific causes were arrived at by onsite investigators, not by arbitrators from the outside.

Indicators from the lab

Numerous laboratory parameters were measured at baseline in the index cohort members. These included interleukin-6 (IL-6), N-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein (CRP), procalcitonin (PCT), troponin T, haemoglobin, erythrocyte mean corpuscular volume, complete leucocyte blood count, iron, hepcidin, ferritin, transferrin Further, we measured the plasma levels of ST2, IL-1 receptor types 1 and 2 (IL-1RT1/IL-1RT2), TNF receptor 2 (TNFR-2), and TNF receptor superfamily members 10c, 13b, and 14 (TNFRSF-10c/-13b/-14). The patient's renal function was assessed using serum creatinine and estimated glomerular filtration rate (eGFR) measurements taken at the start and finish of the experiment. Using a Luminex platform, sandwich or competitive enzyme-linked immunosorbent tests were performed to quantify plasma biomarker concentrations.

Exercise stress testing and echocardiograms

Due to the fact that the majority of patients had previously been examined with conventional echocardiograms one to two months prior to their enrolment in the trial, these data were easily available. These included the size and function of both the left and right ventricles, as well as the thickness of the ventricular wall, the tissue velocities of the lateral and septal annuli, and the diameters of the atrioventricular (AV) annuli. Before a patient was admitted into the study, they had to complete the 6-minute walk test, also known as the 6-MWT.

Quantitative evaluation

SPSS 25.0 was used for all statistical analyses. When displaying non-normally distributed continuous data, the median and interquartile range are used, but when displaying regularly distributed variables, the mean and standard deviation are the appropriate statistical tools to employ (percentage). The baseline characteristics are shown using the quartiles of the IL-6 levels. P 0.05 was taken into consideration as statistically significant. In order to examine the baseline features that differ across the quartiles of IL-6, we performed a one-way analysis of variance (ANOVA), Kruskal-Wallis test, and Chi-square test (where appropriate). At the end of one year, both the primary and secondary outcomes were censored. When doing the analysis of the proportionality of hazards, standardised Schoenfeld residuals were used.

Our objective was to ascertain whether or not IL-6 has the potential to improve previously published risk prediction models applicable to this cohort. Age, recent hospitalisation for heart failure (HF), peripheral oedema, systolic blood pressure, NT-proBNP, hematocrit, HDL cholesterol, salt, and beta-blocker use at baseline all play into the risk score for the primary outcome. The BIOSTAT-CHF risk score for mortality takes into account a number of different factors, including age, blood urea nitrogen, NT-proBNP, haemoglobin, and baseline beta-blocker dosage. Confounding factors were used in our investigation of the relationship between IL-6 and both cardiovascular disease and overall mortality. Our focus was on determining whether or not there was a link between the two. Hospitalizations for heart failure were compared to this competitive

risk, much in the same way that all-cause mortality was used. The possibility for a clinically relevant interaction between the two outcomes was studied. Changes in IL-6 plasma levels were represented as a log2 transformation in all regression models, where a log2 transformation of 1 indicated a doubling of IL-6 plasma levels. We conducted a multivariate logistic regression analysis, which allowed us to establish which variables were most likely to be to blame for the elevated amounts of IL-6 that we found.

Results

The IL-6 plasma levels of four hundred different people were measured. Tables 1 through 4 of the additional material that may be found online provide a comparison between patients who had their baseline IL-6 levels measured and those who did not. In Table 1, the baseline characteristics of the index cohort are shown, including the participants' IL-6 levels. Interleukin-6 (IL-6) levels in patients ranged from 3.1 to 11.21 pg/mL on average, with 228 patients (or 57% of the total) having IL-6 levels that were higher than the 95th percentile of normal values (> 4.45 pg/mL) as previously reported. The average age of the group was 69.85±9.68 years, and there were 295 males in the group (73.75 percent). 17 Patients who had higher levels of IL-6 tended to be older, more frequently suffered from heart failure with preserved ejection fraction (HFpEF), and more frequently suffered from anaemia, diabetes, and atrial fibrillation. Patients who had higher levels of IL-6 also had a greater likelihood of suffering from these conditions (Table 1).

Patients who had higher levels of IL-6 also had a shorter distance travelled during the 6MWT and had a lower chance of completing the test. Both test completion [OR (95% CI) per doubling of IL-6: 0.81 (0.71 - 0.91), P< 0.001] and total distance covered [B (95% CI) per doubling of IL-6: 28.11 (32.58 to - 21.98), P< 0.001] were negatively associated with increasing levels of IL-6, and this remained true after controlling for demographics, comorbidities, medication use, and the New York Heart Association (NYHA) score Patients who had increased levels of IL-6 had significantly lower levels of mean haemoglobin and iron concentrations, somewhat lower levels of transferrin, and a notable drop in transferrin saturation compared to patients who did not have elevated levels of IL-6. There was a statistically significant difference (P <0.001) in the concentration of hepcidin between the quartiles of IL-6, with the first and fourth quartiles having higher concentrations than the middle and third quartiles, respectively (Figure 1).

Patients who had high levels of IL-6 had higher median hepcidin levels than patients who had low levels of IL-6. This was discovered by comparing the two groups' hepcidin levels. There was a correlation between increased levels of IL-6 and increased levels of NT-proBNP and CRP, as well as a reduction in eGFR (Tables 2 and 3 and Figures 2 and 3).

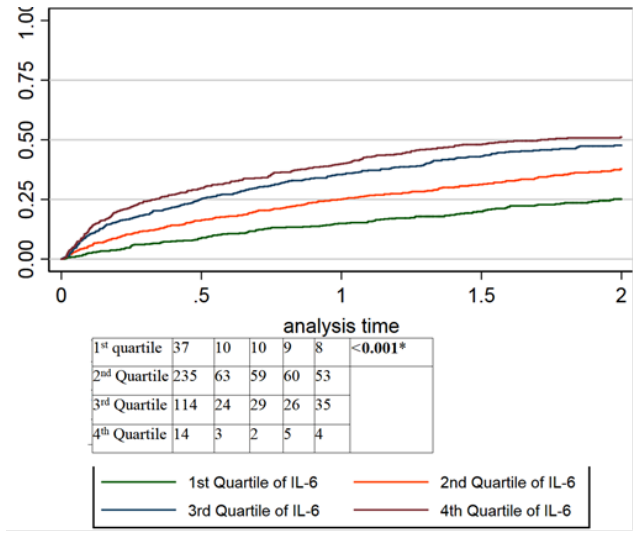

Figure 1. NYHA functional class.

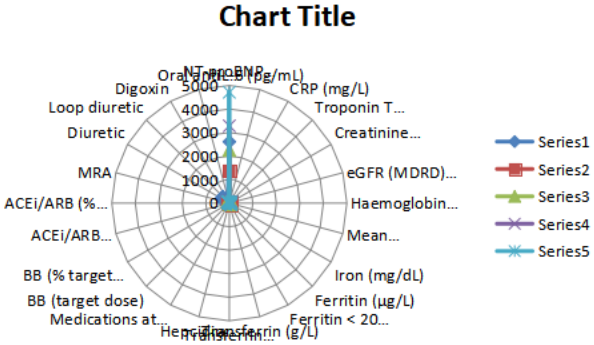

Figure 2. Physical examination of the participants.

Table 1. Basic parameters of the participants.

Parameter	Total =400	Quartile 1=100	Quartile 2=100	Quartile 3=100	Quartile 4=100	*P*-value
Gender						
Male	295	76	72	74	73	0.12
Female	105	24	28	26	27	
Age (years)	69.85±9.68	65.85±7.39	70.36±8.89	69.88±9.64	71.12±7.91	<**0.001***
Distinctive features and comorbidities in the clinical setting						
Primary ischaemic HF aetiology	182	43	45	48	46	0.45
HF hospitalization in previous year	124	30	30	33	31	0.69
Atrial fibrillation	180	36	43	50	51	<**0.001***
Diabetes mellitus	132	27	33	37	35	<**0.001***
Hypertension	252	63	61	69	59	**0.048***
Anaemia	147	22	36	41	48	<**0.001***

Table 2. Physical examination of the participants.

Physical examination BMI (kg/m^2)	28.03±4.36	28.11±5.36	28.15±4.69	28.98±4.22	28.01±4.33	0.22
Heart rate (b.p.m.)	80.25±11.25	76.11±12.36	80.52±12.94	82.25±10.67	85.52±13.32	<**0.001***
Systolic blood pressure	125.52±5.37	127.02±8.36	124.85±7.36	125.02±7.63	122.99±8.36	0.06
Diastolic blood pressure	76.01±9.03	77.04±7.85	76.03±8.36	75.66±7.69	72.98±7.95	<**0.001***
Successful completion of 6MWT	262	83	69	64	46	<**0.001***
6MWT distance	296.52±88.9	349.85±91.6	297.96±95.3	275.88±88.9	232.55±92.36	<**0.001***
LVEF (%)	120	30	30	30	30	0.559
LVEF > 40%	44	6	10	13	15	<**0.001***
e' septal (cm/s)	9.5	9	9	10	10	0.33
Left atrial diameter	8.5	8	8	8	9	0.17

Table 3. Laboratory parameters of the participants.

NT-proBNP (ng/mL)	2610	1375	2255	3285	4712	< **0.001***
IL-6 (pg/mL)	5.5	2.0	4.0	7.0	18.0	<**0.001***
CRP (mg/L)	12.99	5.0	12.0	17.0	28.0	<**0.001***
TroponinT (μg/mL)	0	0	0	0	0	<**0.001***
Creatinine (μmol/mL)	101.58	94.65	101.25	104.85	110.55	<**0.001***
eGFR (MDRD) (mL/min/1.73 m^2)	66	72	66	63	59	<**0.001***
Haemoglobin (g/dL)	13.3	14.0	13.0	12.90	12.80	<**0.001***
Mean corpuscular volume (fL)	91	91	91	90	90	0.35
Iron (mg/dL)	8.0	12.0	10	8.0	7.0	<**0.001***
Ferritin (μg/L)	103.0	112.0	93.0	102.0	106.0	0.06
Ferritin < 20 μg/L	7	7	6	8	5	0.27
Transferrin (g/L)	2.2	2.2	2.2	2.2	2.2	<**0.001***
Transferrin saturation (%)	17.5	24	18	16	12	<**0.001***
Hepcidin (nmol/L) Medications at baseline	6.5	6.8	5.5	5.8	8.6	<**0.001***
BB (target dose)	7	7	6	5	0.31	
BB (% target dose)	1	1	1	1	1	**0.008***
ACEi/ARB	13	17	14	12	9	<**0.001***
ACEi/ARB (% target dose)	1	1	1	1	1	<**0.001***
MRA	215	57	54	55	49	**0.013***
Diuretic	400(100%)	100	100	100	100	0.47
Loop diuretic	400(100%)	100	100	100	100	0.59
Digoxin	75	15	19	18	23	**0.005***
Oral anti-diabetic	251	68	63	61	59	0.22

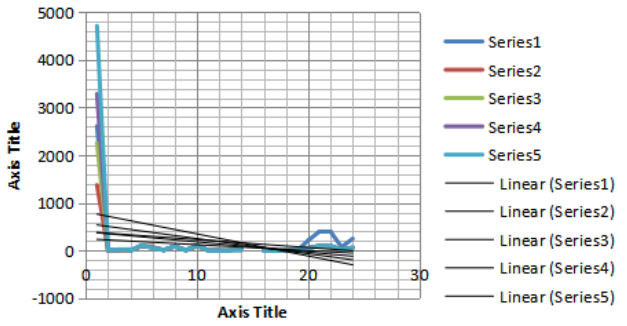

Figure 3. Laboratory parameters of the participant.

Logarithms of NT-proBNP [OR (95% CI): 1.29 (1.09-1.52), P<0.001], PCT [1.28 (1.09-1.49), P< 0.001], reduced iron levels [0.52 (0.42 - 0.58), P<0.001], and hepcidin [1.31 (1.21- 1.51), P<0.001], as well as AF [1.41 (1.11 - 1.49), P<0.001]; Numerous biomarkers linked to TNF-/IL-1, including IL-1RT2, ST2, TNFR-2, TNFRSF-13b, and TNFRSF-14, were also shown to be strong predictors of IL-6. A forest plot is shown for each of the parameters that were considered during the multivariate logistic regression analysis in Table 4 and Figures 4 and 5.

Cox proportional hazards and competing risk survival regression models for the primary and secondary outcomes

Patients whose IL-6 levels were in the highest quartile after one year saw the combined outcome two times as often as those whose IL-6 levels were in the lowest quartile. After taking into account any potentially confounding variables, IL-6 was shown to still be associated with the final result [HR (95% CI): 1.21 (1.09 - 1.32), P 0.001]. Even after taking into consideration the BIOSTAT-CHF risk score, a correlation between higher levels of IL-6 and the composite result was still seen [hazard ratio (95% confidence interval): 1.12 (1.05 - 1.21), P = 0.001]. Increases in IL-6 were associated with higher odds of dying from all causes combined [HR (95% CI): 1.21 (1.14 - 1.32), P 0.001], cardiovascular disease [HR (95% CI): 1.28 (1.21-1.39), P 0.001], and all causes individually [HR (95% CI): 1.19 (1.07-1.31), P 0.001]. IL-6 did not interact substantially with any of the key parameters when attempting to predict the overall result. The cumulative incidence function curves for cardiovascular disease (CV) and non-cardiovascular disease (non-CV) mortality as well as heart failure readmission are shown in the online additional. Between the different quartiles of IL-6, there was not a discernible difference in the patients' risk of dying from cardiovascular disease (CVD) or other causes (P = 0.31). However, IL-6 was not a good predictor of hospitalisations for HF when used by itself (Table 5).

Table 4. Multivariable logistic regression analysis.

Parameter	[OR (95% CI)	P value
NT-proBNP	1.29 (1.09–1.52)	0.001
PCT	1.28 (1.09–1.49)	0.001
lower iron levels	0.52 (0.42 – 0.58)	0.001
hepcidin	1.31 (1.21– 1.51)	0.001
AF	1.41 (1.11 – 1.82)	0.034
older age	0.92 (0.69 – 0.97)	0.041
HFpEF	1.59 (1.12–2.48)	0.031

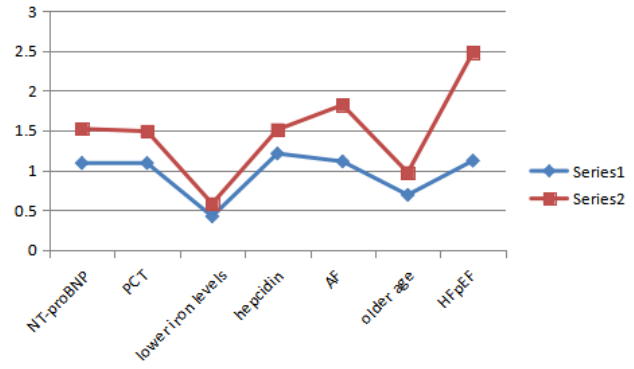

Figure 4. Multivariable logistic regression analysis.

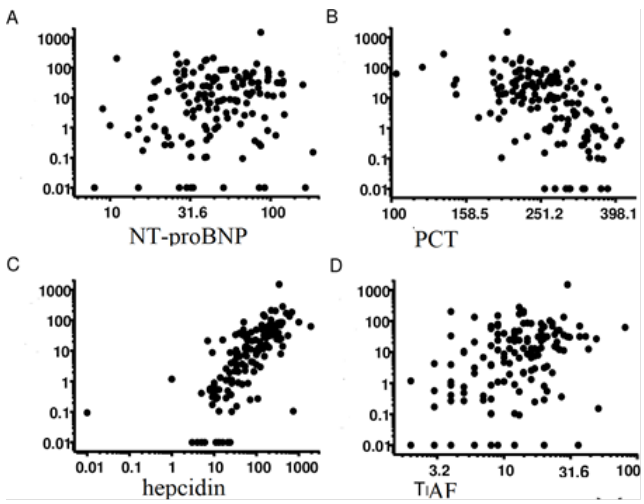

Figure 5. A forest plot is shown for each of the parameters that were considered during the multivariate logistic regression analysis.

NRI>50: 0.5%, P = 0.52; IDI: 0.3%, P = 0.04; Harrell's C base-line: 0.62 vs. Harrell's C IL-6: 0.62 However, there were no significant improvements in discrimination. [NRI>50: 0.5%, P = 0.52; IDI: 0.3%, P = 0.04; Harrell's C base-line: 0.62 vs. Harrell's C The likelihood ratio test showed that interleukin-6 improved the model fit of the

Table 5. Regression models for the primary and secondary outcomes.

	HR (95% CI)	P value
Combined outcome	1.21 (1.09 – 1.32)	0.001
Higher levels of IL-6 remained associated with the combined outcome	1.12(1.05 – 1.21)	0.001
Mortality	1.19 (1.07–1.31)	0.001
Death due to non-CV causes	1.28 (1.21–1.39)	0.001
CV causes	1.21 (1.14 – 1.32)	0.001

BIOSTAT-CHF risk model for the combined outcome (P = 0.003 for the likelihood ratio test). All-cause mortality (Table 5) revealed outcomes that were quite comparable [likelihood ratio test, P 0.001, NRI>50, 0.4%, P = 0.63; IDI, 0.5%, P = 0.03; Harrell's C, baseline, 0.61 vs. Harrell's C, IL-6, 0.65].

Discussion

About half of the individuals in this research had IL-6 levels that were beyond the previously recognised normal limit. Independent predictors of increased IL-6 levels were the presence of HFpEF and AF, being younger, having declining iron values, and increasing PCT, NT-proBNP, TNF-/IL-1, and hepcidin, associated biomarker values. The addition of IL-6 to current predictive models for this population did not enhance risk stratification, despite IL-6's ability to predict all-cause mortality and hospitalisation, as well as all-cause and cause-specific death separately. One possible explanation is that IL-6 is just a predictor of death and hospitalisation from all causes (17).

Our findings suggest that HFpEF is a significant predictor of elevated IL-6 levels. Consistent with earlier research showing that IL-6 and TNF- decrease the expression of sarcoplasmic reticulum Ca2+-ATPase (SERCA2) channels in cardiomyocytes, our results show that IL-6 and TNF- cause a decrease in cAMP levels. These channels are a marker of diastolic dysfunction, and echocardiography can be used to determine whether or not they are functioning properly (18). Calmodulin-dependent protein kinase 2, also known as SERCA2, plays a role in the relaxation of diastolic cardiomyocytes by helping to regulate the reabsorption of calcium from the sarcoplasmic reticulum (18). Additionally, IL-6 causes cardiomyocytes to become more rigid because it inhibits titin phosphorylation (19). It's possible that the processes described above are responsible for the association between IL-6 and malfunction in the diastolic phase of the heart. We discovered that atrial fibrillation was also an independent predictor of elevated IL-6, which is in line with previous research that suggests inflammatory processes more broadly are involved in the aetiology of atrial fibrillation (20).

In contrast to the findings of more recent research6, which indicated higher levels of IL-6 in older patients, high levels of IL-6 were shown to be independently linked with lower ages in this sample. This phenomenon may be explained by changes in IL-6 trans-signaling that occur with ageing. These changes are connected with a decrease in the levels of circulating soluble glycoprotein 130, which is a soluble receptor that suppresses IL-6 activity (21). Due to the fact that IL-6's biological functions may be carried out at lower quantities, it is possible that older persons who have HF have lower amounts of this cytokine. However, due to a lack of data on plasma glycoprotein 130 levels as well as other components of the IL-6 signalling pathway, this notion was unable to be put to the test.

Anemia was more common in patients with elevated IL-6 levels, and there were also shifts in iron metabolism indicators within this group. Patients with greater IL-6 levels also had lower iron levels. Lower iron levels predicted higher IL-6 levels independently. During the acute phase response, triggered by interleukin-6 signalling, the liver produces a protein called hepcidin. This response happens while the liver is fighting off an infection (4, 22). Hepcidin is responsible for hypoferremia, and interleukin-6 is the mediator of this condition (23). IL-6 causes a considerable increase in the amount of hepcidin mRNA that is produced, and this impact is not dependent on either IL-1 or TNF- (22). Anemia in heart failure is associated with a poorer prognosis, but it also impacts a patient's ability to exercise, the development of depression, and maybe even the myocardium itself (24). Previous studies suffered from a lack of association between IL-6 and hepcidin levels in chronic HF; nevertheless, sample sizes were too small to draw any conclusions (24). When taken along with the results of previous studies, our findings suggest the idea that IL-6 signalling might be a valuable therapeutic target for managing anaemia and/or iron deficiency in HF.

In addition, there was a strong correlation between elevated IL-6 levels and elevated NT-proBNP levels. Experiments show that cardiac fibroblasts and cardiomyocytes both produce TNF-/IL-6 and IL-1, and that stretching the heart causes the release of NT-proBNP (19, 25). This result is consistent with the earlier finding that increased levels of TNF and IL-1 related biomarkers are independent predictors of elevated IL-6 levels, as well as with the additional finding that PCT acted as an independent predictor of elevated IL-6 levels. It is widely accepted that the liver is primarily responsible for the production of procalcitonin (PCT), the precursor hormone of calcitonin. Both tumour necrosis factor- and interleukin-6 have the potential to promote the production of acute phase proteins like PCT. Its primary biological activity, which is also the primary biological action of mature calcitonin, is to lower the levels of calcium in the blood (26).

It has been proven that PCT increases the production of inflammatory cytokines by macrophages by acting as a chemokine at damage sites. Macrophages are the major immune cells responsible for the synthesis of IL-6 (27). At the present moment, there is a general assumption that increased PCT levels are associated with infectious processes. This idea is supported by a number of pieces of evidence. However, up to one-third of patients with chronic kidney disease may have a PCT that is abnormally elevated; in these patients, the situation improves when they begin treatment with renal replacement therapy (28). It is possible that PCT has a function in HF as well given that it seems to have a role in illnesses that include chronic inflammation.

IL-6 has been found in a previous study conducted in small cohorts to be a powerful predictor of mortality in patients with acute heart failure, acute coronary syndromes, and chronic heart failure (75 and 102 patients, respectively) (13, 14). It was found that those with elevated plasma IL-6 had a greater risk of mortality, and those with elevated urine IL-6 had a greater risk of having an eGFR that was less than 60 mL/min/1.73 m2. The researchers also found that those with elevated urine IL-6 had a greater risk of having an eGFR that was less than 60 mL/min/1.73 m2 (7). Our study is the first of its kind to incorporate IL-6 in a large enough sample size validated risk prediction model for all-cause mortality and hospitalisation in a worldwide, ethnically and racially diverse HF population. This was accomplished by including IL-6 in a risk prediction model for HF patients. We demonstrated that a rising level of IL-6 was able to independently predict hospitalisation for HF as well as mortality from all causes and specific causes of death. In addition, we demonstrate that a rise in

plasma IL-6 levels is associated with a decrease in eGFR and that this is the case. In spite of this, the risk models that had previously been published for this group were not improved by the inclusion of IL-6.

Implications for clinical practice regarding interleukin-6 and heart failure

Having heart failure with preserved ejection fraction (HFpEF), atrial fibrillation, iron deficiency, and higher levels of NT-proBNP, procalcitonin, hepcidin, and tumour necrosis factor-alpha (TNF-)/interleukin-1 were independently related with having high levels of IL-6 (IL-1). As was mentioned before, earlier fundamental research has shown that the effects of IL-6 are distinct from those of TNF- and IL-1, particularly in regard to iron deficiency (22). These two pieces of information, in conjunction with the findings of a study that showed that prolonged TNF-blocking in rats with HF leads to reactive rises in plasma IL-6, may help explain why TNF-blockade has not been found to exhibit therapeutic advantages in individuals who have HF (29-33). Even though we are unable to make any conclusions about causes and effects from our data, we do feel that there is a need for more studies into the therapeutic applications of IL-6 signalling modulation. IL-6 was a substantial predictor of unfavourable outcomes, but it did not contribute any discriminating power to the current risk models for this group. This is the last but not the least important finding. However, these models also included haemoglobin and NT-proBNP, both of which may fluctuate in conjunction with IL-6 levels and, as a result, account for the fluctuation that is explained by IL-6. It is important to note that these models also included IL-6. Because of the strong link that exists between IL-6 and the iron metabolism indices, we discovered in this study that multicollinearity might lead to incorrect conclusions being drawn from the data (30-33)..

We narrowed the scope of our retrospective analysis by concentrating our attention solely on the relationships that existed between IL-6 plasma levels and a variety of demographic factors, in addition to other inflammatory biomarkers and outcomes. Neither the genetic expression parameters nor any of the other proteomic indicators of IL-6 signalling were understood at that juncture in time. In addition to plasma IL-6, no research was done on any of the other signalling components; these included glycoproteins 130 and the soluble IL-6 receptor. We were unable to explore the association between IL-6 and TNF-/IL-1 in a way that was distinct from one another because we did not have access to longitudinal data on IL-6 levels. This prevented us from being able to investigate the relationship between the two independently of one another.

Additionally, it was not feasible to establish the prevalence of autoimmune illnesses in this community due to the lack of information. In conclusion, despite the fact that a number of correlations were found between IL-6 and clinical measurements or outcomes, more studies will need to be conducted on an individual basis to explore each one in greater detail.

According to the findings of significant research, over half of the patients diagnosed with HF had IL-6 levels that were higher than the 95th percentile of normal values. Independent predictors of IL-6 were younger age, high-flow partial ejection fraction (HFpEF), atrial fibrillation (AF), iron insufficiency, and higher levels of NT-proBNP, PCT, hepcidin, and TNF-/IL-1 related biomarkers. Last but not least, IL-6 levels in the plasma were able to predict death and/or hospitalisation due to HF on their own, despite the fact that they did not contribute to differentiation in prior models. However, in order to further establish causal inferences, it will be necessary for future studies to independently corroborate each of these results.

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